AWARD NUMBER: W81XWH-15-1-0183

TITLE: Early Behavioral Intervention to Improve Social Communication Function in Infants with TSC

PRINCIPAL INVESTIGATOR: Shafali Jeste, MD

CONTRACTING ORGANIZATION: University of California, Los Angeles
Los Angeles, CA 90095

REPORT DATE: October 2016

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	30 Sep 2015 - 29 Sep 2016

4. TITLE AND SUBTITLE

Early Behavioral Intervention to Improve Social Communication Function in Infants with TSC

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0183

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Shafali Jeste, MD, Connie Kasari, Ph.D., Scott Huberty, BA.

E-Mail: shuberty@mednet.ucla.edu; sjeste@mednet.ucla.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of California,
Los Angeles
Los Angeles, CA 90095

Boston Children's Hospital
Division of Developmental Medicine
1 Autumn Street, 6th floor,
Boston, MA, 02215

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Using a collaborative and multi-site model, this project rigorously tests an evidence-based intervention that is developmentally informed, child centered, and focused on early social-communication domains of joint attention and joint engagement. Previous studies from our group have shown that infants with TSC are at high risk for ASD (up to 55%) and that they show signs of ASD as early as 12 months of age. These data motivated us to begin to study the effects of early intervention in these high risk infants using an intervention that has been well studied in toddlers with ASD. Given the paucity of data on the effectiveness of behavioral intervention for infants with TSC, our primary goal is to determine if behavioral and electrophysiological indices of social communication function can be improved with a targeted, short term intervention.
To Date, we have enrolled 7 participants into our study, 3 of whom have completed the intervention. Throughout the next reporting period, we will continue to focus on recruiting and enrolling participants into the study, and monitoring data collection to ensure the highest quality electrophysiological and behavioral data.

15. SUBJECT TERMS
genetic variants, ASD, intervention

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE	Unclassified	14	19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified			

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

Section I – Introduction

This study represents a unique collaboration of experts in neurodevelopmental disorders, developmental cognitive neuroscience, and early intervention research. The innovation, based on this collaboration, lies in (1) the use of biologically based outcome measures and (2) the study of early intervention in an understudied yet high-risk population. Specifically, using a collaborative and multi-site model, this project rigorously tests an evidence-based intervention that is developmentally informed, child centered, and focused on early social-communication domains of joint attention and joint engagement. Given the paucity of data on the effectiveness of behavioral intervention for infants with TSC, our primary goal is to determine if behavioral and electrophysiological indices of social communication function can be improved with a targeted, short term intervention.

In order to identify the mechanisms of change with treatment and to capture subtle changes that may precede behavioral change, we integrate behavioral measures with EEG biomarkers of social communication. The integration of electrophysiology into this study should strengthen our ability to predict outcomes and to gain insight into biomarkers of treatment response in infants at high risk for atypical development.

In addition, we are examining the effects of an experimental intervention (JASPER) on primary (joint engagement) and secondary (joint attention, play, cognition, and parent use of social communication support strategies) outcomes in infants with TSC. Designed by Dr. Kasari and her team, and now studied in hundreds of children with ASD, from high risk infants/toddlers to minimally verbal school-age children, JASPER is a therapist and parent-mediated intervention that (1) targets the foundations of social communication, (2) uses naturalistic behavioral strategies to increase the rate and complexity of social communication and (3) includes parents as implementers of the intervention to promote generalization across settings and to ensure maintenance. JASPER is an ideal treatment for this population because it has shown the most consistent outcomes in improving joint engagement, joint attention and play (core deficits in early ASD) in multiple studies of children with autism spectrum disorder (ASD) and Intellectual Disability (ID) using the most rigorous experimental designs: randomized controlled trials. JASPER will also yield new information on targeted emphases vis-à-vis specific populations, as the regulation components of JASPER may be more emphasized in TSC than other populations, given significant motor and neurological impairments in this population.

We hypothesize that infants in the intervention group will demonstrate significantly better primary and secondary outcomes than infants receiving care as usual during the wait list period, and that we will be able to identify electrophysiological biomarkers of change with treatment in these infants. Furthermore, we believe that there will be a significant interaction between certain baseline characteristics (epilepsy severity, non-verbal cognition, and resting state EEG characteristics) and change in joint engagement and joint attention skills with treatment.

Section II - Keywords:

Genetic variants, ASD, intervention

Section III – Accomplishments

What are the major goals of the project?

AIM 1: To examine the effects of an experimental intervention (JASPER) on primary (joint engagement) and secondary (joint attention, play, cognition, and parent use of social communication support strategies) outcomes in infants with TSC.

AIM 2: To identify electrophysiological biomarkers of change with treatment by examining the effects of JASPER on resting state EEG activity, low level visual processing and face processing.

AIM 3 (exploratory): To characterize baseline clinical, behavioral, and electrophysiological characteristics of children that may predict social communication outcomes.

AIM 4 (exploratory): To determine whether changes in primary and secondary outcomes can be quantified after an initial two-week intensive intervention period.

Major Tasks indicated in the approved Statement of Work			
Major Task	Timeline	Status	Date Completed
Major Task 1: IRB Submission	3 months	Completed	6/23/2015
Major Task 2: Training	6 months	Completed	2/15/2016
Major Task 3: Participant Recruitment, Intervention, Participant Evaluation	24 months	Ongoing	NA
Major Task 4: Prepare Research Protocol For EEG and Behavioral Assessments	2 months	Completed	7/15/2015
Major Task 5: Data analysis	13-24 months	Ongoing	NA

What was accomplished under these goals?

IRB Submission
A thorough explanation of the project aims and protocol were established in local IRB's at each site. IRB's have been updated through amendments as needed. In particular, recent ammendments around modified recruitment strategies were approved, after extensive meetings with the IRB leadership.

Training
We have successfully trained all needed staff in intervention administration, assessment administration, and EEG and Eye tracking data collection. Three staff members across two sites have been trained in the JASPER intervention program, and four staff across two sites have been trained in administration of the *Early Social Communication Scales (ESCS)* and *Structured Play Assessment (SPA)* behavioral assessments. Staff from the BCH site traveled to the UCLA site two separate times to attend trainings from the Kasari lab at UCLA, and since then consistent and immediate feedback

from the Kasari lab has been provided after each session to closely monitor interventionist progress. Bi-weekly conference calls are conducted to discuss study goals, recruitment, and cross-site fidelity. The research protocol for data collection at each time point has been thoroughly documented and implemented across both sites.

Enrollment

Since the grant period began the study teams have successfully recruited 7 families into the project between the two study sites. One participant at the UCLA site has completed the study, and another will complete the intervention during the next reporting period. Additionally, one participant at BCH has completed the study and the second participant will complete intervention in 3 weeks. In addition, the BCH site has recruited a third participant who will come in for their first assessment in the coming weeks. UCLA is currently coordinating with one additional family to schedule screening assessments during the next reporting period.

Recruitment and Outreach

At UCLA in particular, there have been some institutional challenges to recruitment due to competing studies, and this situation has actually led to institution-wide changes in policy and strategy around recruitment of participants that will benefit not only this study but also future studies of TSC at UCLA. . At the UCLA site, Dr. Jeste has worked with the Institutional Review Board to establish a protocol that informs all families who enter the UCLA TSC clinic of studies that their child is eligible for, and it allows them to opt-in to being contacted by the respective study coordinators. This will ensure that all families of children with TSC that come to UCLA are aware of study opportunities for their child. This process will greatly improve all future TSC related studies at UCLA.

Through a close working relationship with the TS Alliance, the study has been publicized on the TS Alliance website and newsletter. The team has worked diligently to increase awareness about the need for early assessment and intervention for these high-risk infants. Each site hosted a recruitment booth at their regional Step Forward and Cure TSC events in Southern California and New England. This is the largest annual TSC community event. The study teams spoke with several interested families and met with community organizers in the TS Alliance regarding coordinating future recruitment events. The UCLA study team and TS alliance are collaborating to hold an educational and recruitment symposium in which Dr. Jeste, Dr. Kasari, and Dr. Bhatt will be speaking to families about the risk of neurodevelopmental delays in TSC and early Intervention in TSC. Dr. Jeste and Dr. Bhatt have presented the study to medical professionals at several community hospitals. In addition to community outreach, both sites have worked with investigators on separate TSC studies to facilitate communication and promotion of all TSC studies to families. At the BCH site, Dr. Sahin who runs a natural history study on infants with TSC, informs families of our intervention study once the infants have completed the natural history study

Additional funding

This study has reinforced the importance of and great need for research in early intervention/early assessment for infants with TSC. The investigators recognize the need for more funding to sustain and expand recruitment, outreach, and intervention for this rare disorder. Therefore, in 2016 Dr. Jeste submitted an application for a NICHD RO1 titled "*Mechanisms of change with early intervention in Tuberous Sclerosis Complex*" to build from the work begun in this study. Current DOD funding has been instrumental in establishing a working relationship in intervention research between BCH and UCLA and in providing the preliminary data required for a larger scale funding mechanism. The RO1 was reviewed on October 20th 2016 and received an extremely high, competitive score (3rd percentile) and is likely to be funded, but we will not have confirmation of this until the budgets are released for 2018.

Research visits completed to date	**10/28/16**				
	V1	V2	V3	V4	
UCLA	4	2	1	1	
BCH	3	2	1	1	
Total	7	4	2	2	
V1 = Entry Assessments. V2 = Post Phase 1 Assessments. V3 = Post Phase 2 Assessments. V4 = Exit Assessments					

The table below describes the overall enrollment of study participants to date:

Demographic information and cognitive scores of participants at Entry							
ID	Sex	Age (months)	Gross Motor Age Equivalent*	Fine Motor Age Equivalent*	Visual Reception Age Equivalent*	Receptive Language Age Equivalent*	Expressive Language Age Equivalent*
01-001	Female	31	9	16	12	14	15
01-002	Male	13	11	9	13	7	8
01-003	Female	25	20	26	26	23	20
01-004	Male	16	10	12	12	13	3
02-001	Male	22	18	20	18	15	18
02-002	Male	37	23	28	33	31	37
02-003	Female	16	-	-	-	-	-

Developments in data analyses

Preliminary EEG and eye tracking data processing

Despite the challenges of collecting EEG and eye tracking data from infants, both study teams have been very successful in acquiring quality data with participants. To demonstrate this point, we have plotted the ERP waveforms for infants enrolled in the study, and eye tracking data for the first infant to complete the JASPER intervention at the UCLA site, acquired during our Social Scenes Paradigm (see Figures 1 & 2). The plot demonstrates that our data collection is of a quality that is already allowing us to see clear gains in attention to faces and social interaction between the pre and post intervention eye tracking sessions. EEG and Eye tracking data quality are continually tracked after research visits to assure that the study teams are collecting sufficient data for future analyses.

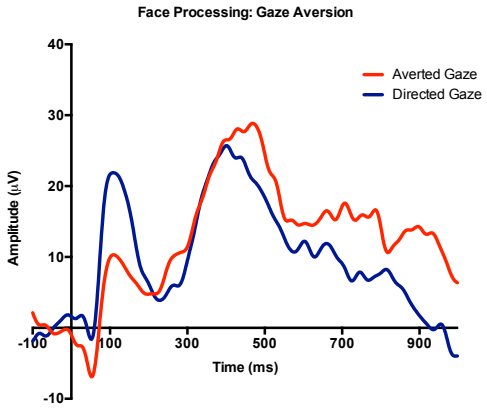

Figure 1

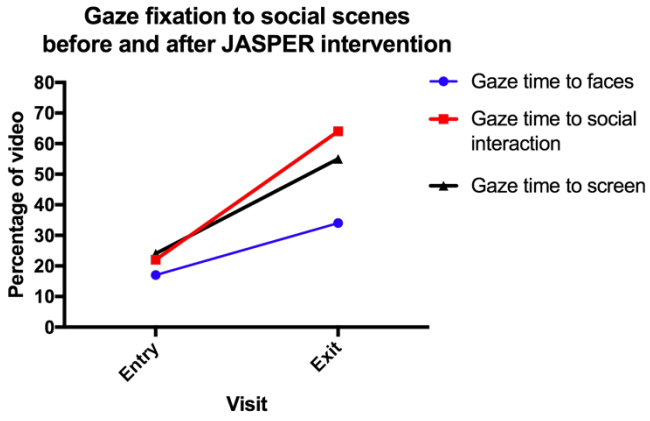

Figure 2

What opportunities for training and professional development has the project provided?

Through the current study, three staff were trained and mentored in the *JASPER* intervention program, and through this training they gained a deeper knowledge of typical and atypical social communication skills. Additionally, through working with children with a rare genetic variant, staff members are gaining insight to the various factors that can impact social communication development, such as hypotonia and other motor impairments, epilepsy, intracranial abnormalities.

How were the results disseminated to communities of interest?

We have been reporting data from our prior DoD study on early markers of ASD in many venues, scientific and community. We have not yet reported data from the JASPER study since we are still in the midst of the trial.

What do you plan to do during the next reporting period to accomplish the remaining goals?

Recruitment will improve now that we have new systems in place at UCLA. In the upcoming reporting period, both sites will continue to actively recruit study participants. The UCLA site will begin an IRB established protocol that informs all families in the TSC UCLA clinic of relevant studies for their child, which will eliminate any barriers to reaching families through the UCLA TSC clinic. UCLA will be hosting a community forum with the TS alliance to discuss TSC and ASD and the benefits of early intervention, and the study teams will continue to work closely with the TS Alliance of Southern California and New England in order to disseminate study flyers and information. BCH and UCLA have partnered with multiple medical centers and community practitioners for support in recruitment for the study.

Section IV – Impact

What was the impact on the development of principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines

Nothing to report.

What was the impact on technology transfer

Nothing to report.

What was the impact on society beyond science and technology

Through this study, we have made an evidence-based treatment more widely accessible to children with a rare genetic syndrome. These children sometimes come from under resourced communities that otherwise struggle to receive services for their children. Additionally, we

received inquiries and interest in participating from several families from out of state, further indicating a nationwide need for individualized intervention for children with rare genetic disorders and high risk for ASD.

The illustrate impact the study has had on families, below is a testimonial provided by the first family that participated in the study at the BCH site:

> *"When we signed up for the TSC JASPER study we were hoping the program would provide a boost to our 22 month-old son's emerging language skills. We received that and so much more!*
> *The program began with an intense portion in which we went to "School with Lauren" every day for two weeks. The play-based sessions challenged our son to stay engaged and expand his play level. He resisted the demands put on him at first, but with each session he extended his attention, made much more eye contact and had great joint attention moments!*
> *At the end of the two weeks we were sad that we would now only be meeting once a week for the next ten weeks, but this gave us more time to work on the routines at home. Being an active part of the therapy sessions and having plenty of time after the sessions to ask questions and learn more about helpful ways to increase all forms of social communication was very motivating and made trying the strategies at home much easier.*
> *The positive changes that we witnessed in our son's behavior made us buy into the therapy completely. Our very talented therapist, Lauren, was so passionate about helping our son that we became a very strong team and made much progress during the sessions.*
> *The four assessments during the study were very comprehensive and conducted with a high degree of professionalism. The feedback we received was very helpful in identifying the areas in which our son needed more support. We even received a consultation with an amazingly talented resource specialist that provided very useful information.*
> *We feel very lucky to have been part of a study that has so many talented and passionate professionals, working hard to improve the outcomes for children like our son. The only negative aspect of the study is that it ended!"*

Section V – Changes/Problems

Changes in approach and reason for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Actual enrollment has fallen behind anticipated enrollment due to an unexpected barrier to recruitment through the UCLA TSC clinic. However, Dr. Jeste has worked closely with the director of the UCLA IRB, and the director of pediatric neurology to create a protocol that informs all families that enter the UCLA TSC clinic of research studies that their child is eligible

for, and allows them to 'opt-in' to being contacted by the study coordinators of the respective studies.

Changes that had a significant impact on expenditures

Nothing to report

Significant change in use or care of human subjects

Nothing to report

Section VI – Products

Publications, conference papers, and presentations

Since funding has started, Dr. Jeste, Dr. Varcin, Dr. Bhatt, and Dr. Nelson have presented at the following meetings and conferences regarding our TSC study:

- Jeste SS (2016). Timing and mechanisms of atypical development in Tuberous Sclerosis Complex: *How early can we detect autism symptoms*?
  2016 FLUX Congress, St Louis MO.

- Jeste, S.S., (2016). Modifying atypical development in Tuberous Sclerosis Complex.
  Kings College London
  London, United Kingdom

- Bhatt R, Hellemann G, Varcin KJ, Nelson CA, Jeste SS, Sahin M, Wu J., (2016). Epilepsy and Cognition in Infants with Tuberous Sclerosis Complex: Can Early Identification of Epilepsy Severity Yield Better Cognitive Outcomes?
  American Academy of Neurology Annual Meeting, 2016
  Vancouver B.C.

- Jeste, SS, Varcin, KV, Hellemann G, Gulsrud, A, Sahin M, Wu, J, Kasari, C, Nelson C. (2016). Symptoms Profiles of Autism Spectrum Disorder in Tuberous Sclerosis Complex.
  American Academy of Neurology Annual Meeting, Scientific Platform Session.
  Vancouver, B.C.

- Varcin, KJ, Jeste, SS, Gulsrud A, Hellemann G, Bhatt R, Kasari C, Nelson CA. (2016). Characterizing early developmental trajectories and social communication profiles in TSC.
  Gatlinburg Conference on Research and Theory in Intellectual and Developmental Disabilities
  San Diego, CA

- Jeste, S.S., (2016). Can rare disorders pave the way to "personalized medicine" in ASD? Lessons learned from Tuberous Sclerosis Complex and Dup15q Syndrome.
  Washington University St. Louis,
  St. Louis, MO

- Jeste, S.S., (2015). Can rare disorders inform targeted interventions for ASD? Insights gained from Dup15q syndrome and Tuberous Sclerosis Complex.
  Boston University Center for Autism Research and Education
  Boston, MA

- Jeste, S.S., (2015). Can rare disorders inform targeted interventions for ASD? Insights gained from Dup15q syndrome and Tuberous Sclerosis Complex.
  Yale Child Study Center
  New Haven, CT

- Varcin, K.J., Jeste, S.S., Nelson, C.A. (2015). Visual social perception in Tuberous Sclerosis Complex.
  International TSC Research Conference
  Windsor, UK.

- Varcin, K.J. Jeste, S.S., Nelson, C.A. (2015). Electrophysiological and behavioral approaches to characterize early development in Tuberous Sclerosis Complex.
  Translational Research Program 'Monthly Autism Meeting' Seminar,
  F.M. Kirby Neurobiology Center, Boston Children's Hospital, Harvard Medical School
  Boston, MA

- Nelson, CA (2015). Perception of Social Stimuli in TSC: Possible Links to Autism.
  Boston LAM-TSC Seminar, Brigham and Women's Hospital
  Boston, MA

Since funding has started, Dr. Jeste, Dr. Varcin, and Dr. Nelson had the following articles regarding the TSC population published:

- Jeste, S.S., Varcin, K.J., Hellemann, G., Gulsrud, A., Bhatt, R., Kasari, C., Wu, J., Sahin, M., Nelson, C.A. (2016). Symptom profiles of autism spectrum disorder in tuberous sclerosis complex. *Neurology*. *87*(8), 766-772. doi:10.1212/wnl.0000000000003002

- Tye, C., Varcin, K.J., Bolton, P. Jeste, S.S. (2016). Early developmental pathways to autism spectrum disorder in tuberous sclerosis complex. *Advances in Autism*.

- Varcin, K.J., Nelson, C.A., Ko, J., Sahin, M., Wu, J. & Jeste, S.S. (2015). Visual evoked potentials as a readout of cortical function in infants with tuberous sclerosis complex. *Journal of Child Neurology.*

- Baker, E. and Jeste, S.S. (2015). Diagnosis and management of Autism Spectrum Disorder in the era of genomics: Rare disorders can pave the way for targeted treatments. *Pediatric Clinics of North America*. epub ahead of print.

Section VI – Participants and other collaborating organizations

What individuals have worked on the project

Person	Role
Shafali Jeste, MD	Principle Investigator (PI)
Connie Kasari, Ph.D.	Co-PI
Charles A. Nelson, Ph.D.	Co-PI
Kandice Varcin, Ph.D.	Research associate
Rujuta Bhatt, MD.	Research Associate
Scott Huberty	Study coordinator
Lauren Baczewski	Interventionist
Alison Holbrook	Interventionist

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to report

Section VIII – Special Reporting Requirements

Nothing to report

Section IX – Appendices

Nothing to report